Journal of Human Hypertension (2006) 20, 765–771

www.nature.com/jhh

ORIGINAL ARTICLE

Differential pulse pressure response to various antihypertensive drug families

EA Karpanou[1], GP Vyssoulis[2], CI Stefanadis[2] and DV Cokkinos[1]
[1]*1st Department of Cardiology, Onassis Cardiac Surgery Center, Athens, Greece and* [2]*1st Cardiology Department of Athens University, Hippokration Hospital, Athens, Greece*

Pulse pressure (PP) is emerging as a major pressure predictor of cardiac disease. The study comprised 10 185 untreated patients with essential hypertension. A total of 5395 men and 4790 women 56 ± 13 years old, with uncomplicated essential hypertension, after a 15-day washout period and after 6 months of antihypertensive monotherapy were included. All patients included in the final cohort were responders and had normalized their blood pressure. PP was decreased least with diuretics (−5 mm Hg) and most with angiotensin II receptor blockers (ARBs) and calcium antagonists (−15 mm Hg), followed by angiotensin-converting enzyme inhibitors (ACEI) (−12 mm Hg) α- and β-blockers (−10 and −9 mm Hg), differentiating among antihypertensive classes ($P<0.001$). The magnitude of PP fall was related to the degree of left ventricular (LV) mass reduction ($P<0.001$), seen best with ARBs ($r=0.42$) and least with ACEIs ($r=0.18$). Of the antihypertensive medications used in everyday practice, PP decrease may be achieved best with ARBs and calcium antagonists, whereas diuretics confer poor response. PP was decreased least with diuretics (−5 mm Hg) and most with ARBs and calcium channel blockers (−15 mm Hg), followed by ACEI (−12 mm Hg) α- and β-blockers (−10 and −9 mm Hg), differentiating among antihypertensive classes ($P<0.001$). Of the antihypertensive medications used in everyday practice, PP decrease may be achieved best with ARBs and calcium antagonists.
Journal of Human Hypertension (2006) **20,** 765–771.
doi:10.1038/sj.jhh.1002069; published online 20 July 2006

Keywords: pulse pressure; left ventricular hypertrophy; antihypertensive drugs

Introduction

Arterial hypertension is well established as an independent and major risk factor for coronary heart disease, stroke, aortic aneurysm and renal failure.[1] Evidence from animal and human studies point out that pulse pressure (PP) correlates positively with carotid atherosclerosis[2] and with white matter lesions.[3] A 20-year follow-up study found that PP is associated with higher mortality in both normotensive and hypertensive subjects.[4] Fang *et al.*[5] proposed that this is true as well for young normotensive persons with low risk of cardiovascular disease.

Analysis of the EURODIAB study showed an association of age with PP in young type I diabetic individuals, stronger in the presence of microvascular complications.[6] The same authors in an other study found that in type II diabetes, PP is positively associated with cardiovascular mortality.[7]

PP can be considered as a marker of an age-associated increase in arterial stiffness, manifested by an increase in systolic (SBP) with parallel decrease in diastolic blood pressure (DBP).[8] Miwa *et al.*[9] reported that PP is an independent and the most powerful predictor of all pressure components of the progress of aortic calcification.

Antihypertensive drug therapy, based on current guidelines, focuses on office measurements of SBP and DBP reduction, but does not offer any advice for PP measurement and effects. The sixth Joint National Committee (JNC-VI) classification system of blood pressure (BP) emphasizes both SBP and DBP, but also mentions that PP may be a risk for cardiovascular disease as well. In the JNC 7 report, while desired SBP and DBP levels are mentioned, no attention to the PP levels is given.[10]

Only few studies have examined the effect of antihypertensive treatment on the magnitude of PP reduction.[11] Similarly, there is a lack of information about the therapy needed to achieve optimal PP values.

The purpose of this study was to evaluate the effect of usual antihypertensive regimens on PP reduction after 6-month therapy, as well as to examine if there is any parallel behaviour of PP and left ventricular (LV) mass regression.

Materials and methods

Study population

We studied retrospectively 11 148 consecutive untreated patients with uncomplicated essential

Correspondence: Dr EA Karpanou, 8, Pavlou Mela Street, Neo Psichiko, Athens 15451, Greece.
E-mail: eva_karpanou@mailbox.gr
Received 30 November 2005; revised 4 June 2006; accepted 4 June 2006; published online 20 July 2006

hypertension, 5939 men and 5209 women 56.1±12.6 years old, from the Hypertension Units of the Cardiology Departments of Athens University and Onassis Cardiac Surgery Center, enrolled through 1986–2004. Patients already on antihypertensive treatment (42%) were evaluated after an at least 15-day wash-out period.

Hypertension was defined according to the JNC 7 criteria as sitting SBP $\geqslant$140 mm Hg and/or DBP $\geqslant$90 mm Hg as measured by sphygmomanometry. A mercury sphygmomanometer was used, with three readings 1 min apart, and the mean value was calculated. PP was defined as the difference between SBP and DBP. Full clinical and laboratory evaluation was carried out in all patients.

Secondary hypertension, acute or chronic inflammatory diseases, endocrinopathies, renal insufficiency (serum creatinine $>$1.5 mg/dl), chronic obstructive or other lung diseases, history of a cerebrovascular event, heart failure, coronary artery disease, type I diabetes mellitus, severe obesity with body mass index (BMI) $>$36 kg/m^2 or inadequate compliance were causes of exclusion from the study. Obesity was defined when BMI was $>$27 kg/m^2. High waist/hips ratio was defined when $>$0.9 in men and $>$0.8 in women. Type II diabetes mellitus and impaired glucose tolerance (IGT) were defined according to the criteria of the American Diabetes Association.

Patients were divided into six groups according to the antihypertensive therapy with thiazide diuretics, β-blockers, α-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and calcium channel blockers (CCBs) (Table 1). To achieve DBP target, drug dosages were uptitrated to the maximally tolerated monotherapy dose, whereas no additional medication was used over the 6 months of the study. Patients with drug-related unwanted effects were dropped from the study. All patients were re-examined bimonthly and re-evaluated after 6 months of antihypertensive monotherapy. The final cohort included patients who normalized their DBP (DBP $<$90 mm Hg or DBP reduction $>$10 mm Hg from baseline). BP before and post-therapy was recorded and the percentage difference (%Δ) in SBP, DBP, PP and LV dimensions were calculated.

Echocardiography study

All patients underwent a complete echocardiographic study on baseline and study end. Patients with no readable echocardiograms were not included in the final cohort. Ultrasound measurements were performed with an ALT Ultramark 8 and 9 apparatus with no knowledge of patient BP levels. LV dimensions and wall thickness were measured from the two-dimensional derived M-mode tracings at the level of the chordae tendineae. The end-diastolic (EDD) and the end-systolic (ESD) diameter, the posterior wall (PW) and the intraventricular septum (IVS) thickness were measured. The measurements were obtained according to the Penn convention criteria. LV mass was calculated according to Devereux *et al*.[12] and was corrected by body surface area (BSA): LV mass index (LVMI)$=$ $1.04((\mathrm{EDD}+\mathrm{IVS}+\mathrm{PW})^3)-\mathrm{EDD}^3)-13.6/\mathrm{BSA}$, and by body height raised to the 2.7 power. The reproducibility of LV volume measurement in our laboratory is high, with an interobserver variability less than 5% and intraobserver variability $<$3%, with r values in the order of 0.98.

Statistics

Continuous variables are presented as mean values±s.d., while qualitative variables are presented as absolute and relative frequencies. Univariate analysis was initially applied to test the associations of difference of LVMI with the difference of PP as well as the associations between various characteristics of the participants and both the outcome and main effect of interest. Comparisons between normally distributed continuous variables and categorical variables were made using the Student's t-test. Correlations between normally distributed continuous variables were evaluated by calculating the Pearson's r-coefficient. The associations between difference of LVMI (dependent variables) and difference of PP were also tested through multiple linear regression analysis. The results obtained from the regression models are presented as β-coefficients and the 95% confidence intervals of the coefficient of the difference of PP. The explanatory variables entered in each multivariate model were: (a) the variables that showed a significant association with

Table 1 Patient characteristics according to the antihypertensive treatment used

Rx	*Diuretics*	β-*Blockers*	α-*Blockers*	*ACEIs*	*ARBs*	*CCBs*
N (males%)	592 (46.3)	2427 (52.9)	470 (49.6)	2328 (53.9)	1961 (56.2)	3370 (53.1)
Smokers (%)	177 (29.9)	836 (34.4)	136 (28.9)	805 (34.6)	527 (26.9)	1035 (30.7)
IGT (%)	85 (14.4)	374 (15.4)	86 (18.3)	392 (16.8)	404 (20.6)	502 (14.9)
Type II DM (%)	75 (12.7)	145 (6.0)	79 (16.8)	320 (13.7)	268 (13.7)	512 (15.2)
Obese (%)	319 (53.9)	1238 (51.0)	282 (60.0)	1329 (57.1)	1188 (60.6)	1932 (57.5)
Age (years)	58.3±12.0	49.8±11.5	59.7±10.9	54.4±12.2	58.8±12.9	59.5±11.7
High W/H ratio (%)	335 (56.6)	1110 (45.7)	296 (63.0)	1417 (60.9)	995 (50.7)	2174 (64.7)

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; DM, diabetes mellitus; IGT, impaired glucose tolerance.

Table 2 BP and heart rate values before and after treatment

	N	*Diuretics (592)*	β-*Blockers (2427)*	α-*Blockers (470)*	*ACEIs (2328)*	ARBs (1961)	*CCBs (3370)*
Before	SBP	159.9±12.9	157.1±13.2	163.9±13.5	162.5±14.7	166.0±14.0	168.8±15.0
	DBP	99.8±6.6	103.3±5.2	99.1±6.5	102.2±7.2	100.8±7.9	101.2±8.4
	PP	60.2±15.9	53.8±14.0	64.9±16.2	60.4±16.7	65.2±17.2	67.5±17.4
	HR	74.2±8.5	82.2±9.8	72.4±9.0	74.9±8.9	73.7±6.8	72.6±9.7
After	SBP	136.8±10.0	129.3±10.1	137.4±11.0	132.2±10.6	131.4±9.0	135.0±10.7
	DBP	81.9±6.9	84.5±4.7	82.6±7.0	83.9±5.9	81.6±5.3	82.4±6.5
	PP	54.9±12.5	44.7±9.7	54.8±12.0	48.3±11.2	49.9±11.0	52.6±11.5
	HR	75.3±7.4	68.3±6.0	72.3±7.1	73.1±7.4	74.2±5.9	73.3±7.8
Difference	SBP	−23.1±10.5	−27.8±10.7	−26.5±11.3	−30.4±11.2	−34.5±10.3	−33.7±12.8
	DBP	−17.8±5.6	−18.7±5.1	−16.5±5.6	−18.3±5.5	−19.2±5.4	−18.8±6.2
	PP	−5.3±10.5	−9.1±10.0	−10.0±10.5	−12.1±10.5	−15.3±10.4	−14.9±12.3
	HR	1.0±5.1	−14.0±9.8	−0.0±6.8	−1.8±4.3	0.4±3.1	0.7±7.6
%Δ	SBP	−17.1±8.4	−21.8±8.9	−19.6±8.9	−23.2±9.0	−26.4±8.0	−25.3±10.4
	DBP	−22.2±8.4	−22.3±8.9	−20.4±8.9	−22.0±9.0	−23.6±8.0	−23.1±10.4
	PP	−6.4±16.3	−14.6±15.8	−13.7±14.2	−17.9±14.3	−21.7±12.2	−19.9±14.9
	HR	1.8±6.6	−16.2±10.0	0.6±8.9	−2.1±5.5	0.8±4.2	1.8±10.1

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BP, blood pressure; CCBs, calcium channel blockers; DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure.

dependent variables in univariate analysis (at 15% significance level); (b) those associated with LVMI and (c) various first-order interactions with the LVMI. All models were adjusted for age, gender, smoking (in pack-years), BMI, creatinine, BP and diabetes mellitus history. A backward elimination procedure was applied to all multivariate models, using $P<5\%$ as the threshold for removing a variable from the models. Normality tests were applied using the Kolmogorov–Smirnov criterion as well as Shapiro–Wilk test. Creatinine levels were log-transformed owing to their skewed distributions. PP as well as age and BMI were distributed normally. The assumptions of linearity for continuous independent variables and constant variance of the standardized residuals were assessed by plotting the residuals against fitted values. We also calculated r^2 to determine how well each fitted model predicts the dependent variables. All reported *P*-values are based on two-sided tests and compared to a significance level of 5%. STATA 8.0 software (Stata Corporation. 2003, College Station, TX, USA) was used for all statistical calculations.

Results

Our study patients were classified into the abovementioned six groups according to the antihypertensive therapy (Table 1). The male/female ratio as well as the habit of smoking, incidence of IGT and type II diabetes mellitus were similar in the six treatment groups, although patients on β-blockers were younger and on calcium antagonists were older ($P<0.001$).

BP and heart rate values before and after treatment are shown in Table 2. Maximal SBP and DBP fall was observed in patients who received either ARBs or CCBs followed by ACEIs, diuretics, β-blockers and α-blockers ($P<0.001$). Maximal PP fall was observed in patients who received either ARBs or CCBs (−15 mm Hg) and followed by ACEIs (−12 mm Hg), whereas PP reduction with diuretics ($P<0.001$) was smaller (−5 mm Hg). ARBs and CCBs did not differ as regards PP fall ($P=$NS), as did α- and β-blockers. The magnitude of BP fall with the six ARBs used was uniform ($P=$NS), as shown in Table 3.

LVMI values and changes before and after treatment are shown in Table 4. ACEIs and ARBs achieved the greatest LVMI reduction (−13%) followed by CCBs, whereas α- and β-blockers achieved moderate LVMI regression, and diuretics were the least effective in LVMI reduction (−2.7%). Results were similar, using the LVM/$H^{2.7}$ index. Again, all these differences were significant ($P<0.0001$).

The magnitude of LV hypertrophy regression was related ($P<0.0001$) to PP fall in all drug groups (Table 5 and Figure 1). The strongest relation was seen in the ARB group ($r=0.42$) and the weakest in the ACEI group ($r=0.18$), whereas all the other drug groups had intermediate relationships. These relationships remained significant after correction for confounders in multifactorial analysis. LV hypertrophy regression was related to SBP and PP fall, although it was not related to DBP reduction.

Discussion

Our data show that antihypertensive medications used in every day practice have different effect on PP decrease, achieving the best result with ARBs and CCBs, while PP fall magnitude was related to the degree of LV mass reduction. Data from the Framingham study restricted to persons over 50

Table 3 BP and HR values before and after treatment with six ARBs

	N	*Candesartan (364)*	*Eprosartan (125)*	*Irbesartan (422)*	*Losartan (527)*	*Telmisartan (207)*	*Valsartan (316)*
Before	SBP	165.5±14.0	163.7±11.1	167.2±15.3	166.2±13.8	166.4±14.6	165.1±12.9
	DBP	101.2±8.4	99.7±7.3	101.4±8.8	100.6±7.2	100.3±7.8	100.5±7.3
	PP	64.3±17.9	64.0±16.9	65.8±18.0	65.6±16.5	66.1±18.2	64.6±16.1
	HR	73.8±7.1	72.4±5.2	74.2±6.6	74.4±7.4	72.9±5.9	73.1±6.5
After	SBP	129.9±9.4	130.1±8.5	132.3±8.5	132.2±9.2	132.2±8.9	130.9±8.9
	DBP	81.5±5.3	81.1±4.7	81.9±5.5	81.6±5.5	81.6±5.2	81.5±5.4
	PP	48.4±11.7	49.0±10.2	50.4±10.6	50.7±11.1	50.6±11.2	49.4±10.7
	HR	74.3±5.9	72.2±4.6	74.8±5.7	74.6±6.4	73.2±5.3	73.8±5.9
Difference	SBP	−35.6±10.0	−33.6±8.1	−35.0±10.9	−34.0±10.4	−34.2±10.8	−34.2±9.8
	DBP	−19.7±5.8	−18.6±5.1	−19.5±6.1	−19.0±5.0	−18.7±5.6	−19.0±4.8
	PP	−15.9±10.3	−15.0±9.7	−15.5±10.7	−15.0±10.4	−15.4±11.4	−15.2±9.9
	HR	0.5±3.0	−0.2±3.0	0.2±3.0	0.2±3.6	0.3±3.0	0.8±2.6
%Δ	SBP	−25.7±8.0	−25.9±6.5	−26.5±8.0	−25.8±8.4	−25.9±8.3	−26.3±8.0
	DBP	−24.2±7.2	−23.0±6.5	−23.9±7.4	−23.4±6.6	−23.1±7.1	−23.3±6.1
	PP	−22.7±13.8	−21.4±13.1	−21.3±11.9	−21.3±11.4	−21.4±12.2	−22.1±11.8
	HR	0.9±4.0	−0.2±4.1	1.0±3.9	0.5±4.8	0.6±3.9	1.2±3.6

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure.

Table 4 LV mass corrected for body surface area (LVMI) or $H^{2.7}$ values before and after treatment

	Diuretics	β-*Blockers*	α-*Blockers*	*ACEIs*	*ARBs*	*CCB*
Before						
LVMI	137.3±18.7	134.0±16.2	139.9±18.9	142.3±20.0	139.8±20.8	144.9±21.2
LVM/$H^{2.7}$	65.1±11.8	62.1±10.3	66.8±12.2	67.2±13.0	66.0±12.6	69.0±13.5
After						
LVMI	133.4±18.1	124.9±14.8	129.0±16.4	123.5±16.0	120.9±15.1	128.6±16.3
LVM/$H^{2.7}$	62.9±11.2	57.7±9.5	61.5±10.7	58.2±10.7	57.1±9.7	61.0±10.6
Difference						
LVMI	−3.8±6.2	−9.2±6.5	−10.9±7.8	−18.8±8.6	−18.8±8.2	−16.3±9.4
LVM/$H^{2.7}$	−2.2±3.0	−4.4±3.0	−5.3±3.9	−9.0±4.3	−8.9±4.1	−8.0±4.8
%Δ						
LVMI	−2.7±4.3	−6.7±4.3	−7.5±4.9	−13.0±4.8	−13.1±4.3	−10.8±5.2
LVM/$H^{2.7}$	−3.2±4.2	−6.9±4.3	−7.7±4.9	−13.1±4.9	−13.1±4.2	−11.1±5.3

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers, LV; left ventricular; LVMI, left ventricular mass index.
All, $P<0.001$.

Table 5 Univariate correlation coefficient values of LVMI and PP reduction, and *β*-coefficients of multifactorial regression

	Univariate r *values*	β-*Coefficients*	*Confidence intervals*
Diuretics	0.228	0.135	0.088–0.182
β-Blockers	0.224	0.147	0.122–0.172
α-Blockers	0.250	0.188	0.122–0.254
ACEIs	0.182	0.167	0.131–0.203
ARBs	0.421	0.301	0.268–0.334
CCBs	0.287	0.158	0.130–0.185

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers.
All, $P<0.001$.

years old showed that the association with coronary heart disease risk, although positive both for SBP and DBP, was strongest for PP.[13]

Domanski *et al.*,[14] reported that cardiovascular disease risk assessment is improved by considering simultaneously both SBP and DBP, not just SBP, DBP or PP separately. On the other hand, results of a large prospective cohort study indicate a great complexity in the relationship of PP with mortality, depending on age and interactions with both SBP and DBP, and thus discouraging its use for prognostic or therapeutic decisions.[15]

Nevertheless, a meta-analysis of three trials in older subjects has shown that PP but not mean BP is the major determinant of cardiovascular risk.[16]

Taking into account the fact that all studies till now have demonstrated the importance of PP in the determination of cardiovascular risk, the choice of the best antihypertensive regimen for optimal PP reduction is very significant. Our study agree with that of Takami *et al.*[11] who demonstrated that ARBs

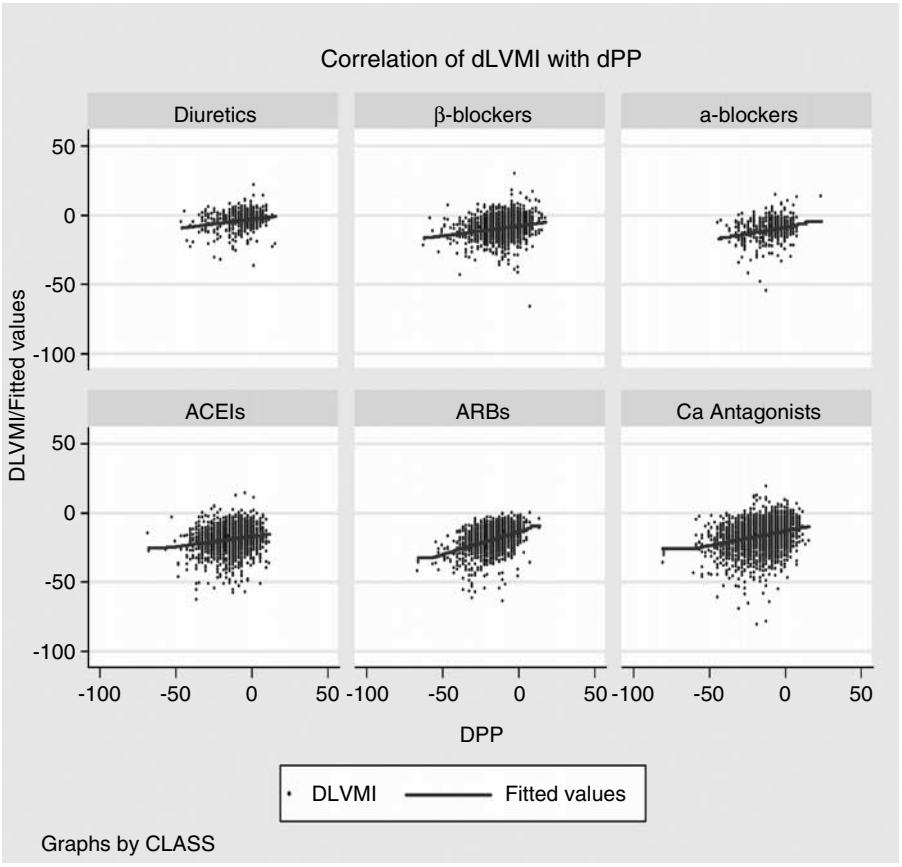

Figure 1 Correlations of LVMI and PP reduction with the six-drug regimens.

yielded the largest reduction in PP, followed by the ACEI and N-type CCBs.

Additionally, PP has been shown to predict LV hypertrophy[17,18] and target organ damage in essential hypertension, whereas its increase is accompanied by higher risk of heart failure.[19] In patients with a low LV ejection fraction, PP is a strong predictor of myocardial infarction,[20] cardiovascular and all-cause mortality.[21] In the Balloon Angioplasty Revascularization Investigation (BARI) study, an independent association of PP and total mortality after revascularization was found.[22] Furthermore, findings of the multicentre ESCAPP study showed that aortic PP was significantly related to the presence and extent of coronary artery disease in patients without antihypertensive therapy.[23]

It is surprising that in various mega trials addressing the performance of various treatment modalities for hypertension, their influence on PP is not taken into account. Currently, the choice of the drug for the initial treatment of hypertension is very strongly debuted. Although ARBs have been shown superior to β-blockers in the LIFE study[24] and ACEI better than diuretics in the Captopril Prevention Project (CAPPP) trial,[25] these findings have not been confirmed. On the contrary, the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) results suggest that chlorothalidone was better than lisinopril, both in lowering BP and diminishing cardiovascular events, but no differential effects of drug class on PP were found when all participants were considered.[26] In the Hypertension Optimal Treatment (HOT) study, only the degree of DBP reduction was used to assess cardiovascular outcomes.[27]

An analysis of the NHANES III did not detect any difference in PP fall for any medication class compared with the referent β-blocker group after adjustment for covariates, but in the subgroup of subjects over 72 years, diuretics decreased PP most.[28] In the REASON study, Pannier *et al.*[29] found that a very low-dose perindopril/indapamide combination decreases SBP and PP to a larger extent than does a β-blocker after a 12-month treatment. Polonia *et al.*[30] found that ACEIs or ARBs appear to have a more favourable profile on aortic stiffness, central pressures and aortic wave reflection comparing to β-blockers and CCBs.

The present study agrees with the above beneficial actions of renin-blocking drugs and calcium antagonists, but does not confirm the superiority of diuretics on PP reduction. This may probably be owing to the relative short duration and the retrospective character of the study. In addition, the

population of this study was relatively young with mostly combined systolic and diastolic hypertension. This means that arterial stiffness was probably not prominently present. An older population with increased arterial stiffness may have responded better with diuretic therapy.

Our study can be considered interesting, as guidance for drug choice for effective PP reduction leading to LV hypertrophy regression and arterial stiffness improvement in high-risk hypertensives. This view is enhanced by the new perspective of de Simone *et al.*[31] who recently proposed that PP is a sign of target organ damage rather than a traditional cardiovascular risk factor.

What is known on this topic
- PP is a marker of target organ damage in arterial hypertension and is associated with cardiovascular mortality.
- Guidelines on antihypertensive management focus on SBP and DBP, ignoring PP.

What this study adds
- PP reduction is achieved best with ARBs and CCBs.
- PP reduction is related to LVM regression, seen best with ARBs.

Abbreviations: ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; DBP, diastolic blood pressure; LVM, left ventricular mass; PP, pulse pressure; SBP, systolic blood pressure.

References

1 Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA *et al.* Blood pressure, stroke and coronary heart disease. Part 2. Short term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. *Lancet* 1990; **335**: 827–838.
2 Franklin SS, Sutton-Tyrrell K, Belle SH, Weber MA, Kuller LH. The importance of pulsatile components of hypertension in predicting carotid stenosis in older adults. *J Hypertens* 1997; **15**: 1143–1150.
3 Liao D, Cooper L, Cai J, Toole J, Bryan N, Burke G *et al.* The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC study. *Neuroepidemiol* 1997; **6**: 149–162.
4 Benetos A, Rudnichi A, Safar M, Guize L. Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. *Hypertension* 1998; **32**: 560–564.
5 Fang J, Madhavan S, Alderman MH. Pulse pressure: a predictor of cardiovascular mortality among young normotensive subjects. *Blood Pressure* 2000; **9**: 260–266.
6 Schram MT, Chaturvedi N, Fuller JH, Stehouwer CD. Pulse pressure is associated with age and cardiovascular disease in type 1 diabetes: the Eurodiab Prospective Complications Study. *J Hypertens* 2003; **21**: 2035–2044.
7 Schram MT, Kostense PJ, van Dijk RAJM, Dekker JM, Nijpels G, Bouter LM *et al.* Diabetes, pulse pressure and cardiovascular mortality: the Hoorn Study. *J Hypertens* 2002; **20**: 1743–1751.
8 Van Bortel L, Struijker-Boudier H, Safar ME. Pulse pressure, arterial stiffness, and drug treatment of hypertension. *Hypertension* 2001; **38**: 914–921.
9 Miwa Y, Tsushima M, Arima H, Kawano Y, Sasaguri T. Pulse pressure is an independent predictor for the progression of aortic wall calcification in patients with controlled hyperlipidemia. *Hypertension* 2004; **43**: 536–540.
10 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL *et al.* Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee: seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; **42**: 1206–1252.
11 Takami T, Shigemasa M. Efficacy of various antihypertensive agents as evaluated by indices of vascular stiffness in elderly hypertensive patients. *Hypertens Res* 2003; **26**: 609–614.
12 Devereaux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977; **55**: 613–618.
13 Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation* 1999; **100**: 354–360.
14 Domanski MJ, Davis BR, Pfeffer MA, Mitchell Gf. Isolated systolic hypertension. Prognostic information provided by pulse pressure. *Hypertension* 1999; **34**: 375–380.
15 Pastor-Barriuso R, Banegas JR, Damian J, Appel LJ, Guallar E. Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. *Ann Intern Med* 2003; **139**: 731–739.
16 Blacher J, Safar ME. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive subjects. *Arch Intern Med* 2000; **160**: 1085–1089.
17 Pannier B, Brunel P, el Aroussy W, Lacolley P, Safar ME. Pulse pressure and echocardiographic findings in essential hypertension. *J Hypertens* 1989; **7**: 127–132.
18 Khattar RS, Acharya DU, Kinsey C, Senior R, Lahiri A. Longitudinal association of ambulatory pulse pressure with left ventricle mass and vascular hypertrophy in essential hypertension. *J Hypertens* 1997; **15**: 737–743.
19 Chae CU, Pfeffer MA, Glynn RJ, Michell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. *JAMA* 1999; **281**: 634–639.
20 Mitchell GF, Moye LA, Braunwald E, Rouleau JL, Bernstein V, Geltman EM *et al.* Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and Ventricular Enlargement. *Circulation* 1997; **96**: 4254–4260.
21 Domanski MJ, Mitchell GF, Norman JE, Exner DV, Pitt B, Pfeffer MA. Independent prognostic information provided by sphygmomanometrically determined pulse pressure and mean arterial pressure in patients with left ventricular dysfunction. *J Am Coll Cardiol* 1999; **33**: 951–958.
22 Domanski MJ, Sutton-Tyrrell K, Mitchell GF, Faxon DP, Pitt B, Sopko G. Balloon Angioplasty Revascularization Investigation (BARI). Determinants and prognostic information provided by pulse pressure in patients with coronary artery disease undergoing revascular-

ization. The Balloon Angioplasty Revascularization Investigation (BARI). *Am J Cardiol* 2001; **87**: 675–679.
23 Danchin N, Benetos A, Lopez-Sublet M, Demicheli T, Safar M, Mourad JJ. ESCAPP Investigators. Aortic pulse pressure is related to the presence and extent of coronary artery disease in men undergoing diagnostic coronary angiography: a multicenter study. *Am J Hypertens* 2004; **17**: 129–133.
24 Dahlof B, Devereaux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U *et al.* LIFE Study Group. Cardiovascular morbidity and mortality in the Losardan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002; **359**: 995–1003.
25 Hansson L, Lindholm LH, Niskaen L, Hedner T, Niklason A, Luomanmaki K *et al.* Effect of angiotensin converting enzyme inhibitor compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomized trial. *Lancet* 1999; **353**: 611–616.
26 The ALLHAT officers coordinators for the ALLHAT collaborative research group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorothalidone; the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT). *JAMA* 2000; **283**: 1967–1975.
27 Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S *et al.* Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. *Lancet* 1998; **351**: 1755–1762.
28 Chang JJ, Luchsinger JA, Shea S. Antihypertensive medication class and pulse pressure in the elderly: analysis based on the Third National Health and Nutrition Examination Survey. *Am J Med* 2003; **115**: 536–542.
29 Pannier B, Guerin A, London G, Asmar R, Safar M. Combination of low dose Perindopril/Indapamide versus Atenolol in the hypertensive patient. Effects on systolic blood pressure and arterial haemodynamics. The REASON study. *Arch Mal Coeur* 2002; **95**: 11–16.
30 Polonia J, Barbosa L, Silva JA, Maldonado J. Different influences on central and peripheral pulse pressure aortic wave reflections and pulse wave velocity of three different types of antihypertensive drugs. *Rev Port Cardiol* 2003; **22**: 1485–1492.
31 de Simone G, Roman MJ, Alderman MH, Galderisi M, de Divitiis O, Devereaux RB. Is high pulse pressure a marker of preclinical cardiovascular disease? *Hypertension* 2005; **45**: 575–579.